

PATENT SPECIFICATION

(11) 1276 966

NO DRAWINGS

9969221

- (21) Application No. 55314/70 (22) Filed 20 Nov. 1970
 (31) Convention Application No. 879619 (32) Filed 24 Nov. 1969 in
 (33) United States of America (US)
 (45) Complete Specification published 7 June 1972
 (51) International Classification C07C 87/02 91/00 93/00 95/08 97/10
 101/42 103/00 123/00 C07D 13/10 23/06 25/00
 27/00 27/04 27/56 29/26 99/04



(52) Index at acceptance

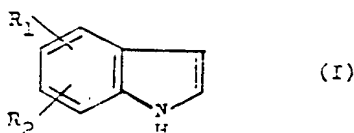
C2C 171—191—280 172—194—284 174—198—272
 191—194—196 200 213 215 220 221 225 226 227
 22Y 246 247 250 251 253 255 25Y 273—280—287
 305 30Y 311 313 31Y 323 32Y 332 337 338 350
 364 366 368 36Y 3A10E3D1 3A10E5E 3A13C10H
 3A13C1C 3A13C4C 3A13C6C 3A5C1C2 3A5F5
 470 471 500 50Y 620 621 624 650 661 671 681
 697 698 69Y 708 776 LP LW MK ML MM ZF ZG

(54) A PROCESS FOR THE MANUFACTURE OF INDOLES, A
 PROCESS FOR THE PREPARATION OF
 ORTHO-NITRO- β -AMINOSTYRENES USEFUL THEREIN
 AND CERTAIN ORTHO-NITRO- β -AMINOSTYRENES *PER SE*

(71) We, F. HOFFMANN-LA ROCHE & CO., AKTIENGESELLSCHAFT, a Swiss Company of 124—184 Grenzacherstrasse, Basle, Switzerland, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

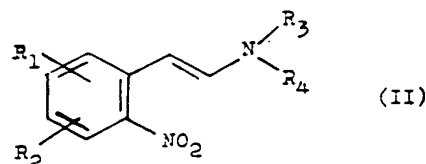
The present invention is concerned with a process for the manufacture of indoles. It is also concerned with a process for the preparation of *ortho*-nitro- β -aminostyrenes useful in said process and with certain of said *ortho*-nitro- β -aminostyrenes *per se*.

The indoles obtained according to the present invention have the general formula



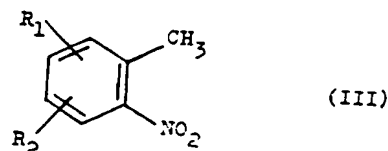
wherein R_1 and R_2 independently represent hydrogen, lower alkyl, aryl, hydroxy, lower alkoxy, aryl-lower alkoxy, aryloxy, acyloxy, formyl, aroyl, hydroxymethyl, aryl-hydroxymethyl, carboxy, lower alkoxycarbonyl, carbamoyl, halogen, amino, mono-lower alkyl-amino, di-lower alkylamino, lower alkoxy-carbonylamino, aryl-lower alkoxy-carbonylamino, acylamino, N-lower alkylacylamino, di-lower alkylformamidino, or di-lower alkoxymethyl or R_1 and R_2 together represent lower alkylenedioxy.

According to one embodiment of this invention, the indoles of formula I hereinbefore are manufactured by treating an *ortho*-nitro- β -aminostyrene of the general formula



wherein R_1 and R_2 have the significance given earlier and R_3 and R_4 independently represent lower alkyl or R_3 and R_4 together represent lower alkylene, with a reducing agent.

According to another embodiment of this invention, the *ortho*-nitro- β -aminostyrenes of formula II hereinbefore are prepared by condensing an *ortho*-nitrotoluene of the general formula



wherein R_1 and R_2 have the significance given earlier,

BEST AVAILABLE COPY

invention involves condensing the methyl function of an *ortho*-nitro-toluene with the formyl radical of a formamide acetal to yield a nitrobenzene derivative which bears a N,N-disubstituted aminovinyl function in the *ortho*-position to the nitro group and thereafter reducing the nitro group to an amino group with concurrent displacement of the N,N-disubstituted amino function and cyclization to form an indole nucleus.

The *ortho*-nitrotoluenes of formula III are known or can be prepared by known procedures. Examples of such *ortho*-nitrotoluenes are 3 - methyl - 4 - nitrobiphenyl, 2 - methyl - 3 - nitrobenzyl alcohol, 3 - nitro- *p* - toluamide, 4 - methyl - 3 - nitrobenzophenone, 3 - nitro - *p* - toluic acid methyl ester, N,N - dimethyl - 3 - nitro - *p* - toluidine, 3 - nitro - *p* - toluic acid, 4 - methyl - 3 - nitrobenzophenone, N - methyl - 3 - nitro - *p* - toluidine and 3 - nitro - *p* - toluidine.

The formamide acetals of formula IV are known or can be prepared by known procedures. A preferred group of formamide acetals of formula IV comprises, for example, N,N - dimethylformamide diethyl acetal, N,N-dimethylformamide dimethyl acetal, N-formylpyrrolidine dimethyl acetal, 2-dimethylamino - 1,3 - dioxolane, N - formyl - piperidine dimethyl acetal, N,N-dimethylformamide dibenzyl acetal, N,N-dimethylformamide dicyclohexyl acetal, N,N-dimethylformamide dincopentyl acetal, N,N-dimethylformamide diisopropyl acetal and N,N-dimethylformamide di-*n*-heptyl acetal.

The condensation of an *ortho*-nitrotoluene of formula III with a formamide acetal of formula IV can be carried out in the presence or absence of an inert organic solvent. Preferably, the condensation is carried out in the presence of a polar aprotic solvent such as, for example, N,N-dimethylformamide (DMF), diethyleneglycol dimethyl ether (diglyme) and hexamethylphosphortriamide (HMPT). The conditions employed for the condensation are not narrowly critical. Thus, the condensation can be carried out at a temperature in the range of from room temperature to the reflux temperature of the condensation mixture. Preferably, the condensation is carried out at a temperature in the range of from 100°C to 160°C. Most conveniently, the condensation is carried out at the reflux temperature of the condensation mixture. The condensation may be carried out at atmospheric or super-atmospheric pressures. Conveniently, it is carried out at atmospheric pressure.

In a preferred aspect of this process, R₁ and R₂ each represents methyl, and one of R₁ and R₂ represents hydrogen and the other represents hydrogen or methyl in the 3-position.

The *ortho*-nitro- β -aminostyrenes of formula II are reduced chemically or catalytically to yield the corresponding indole deri-

vatives of formula I. The catalytic reduction may be carried out in any conventional manner, but it is preferably carried out at about room temperature with a hydrogen pressure of from 1 to 10 atmospheres. Any suitable hydrogenation catalyst may be employed. Examples of suitable hydrogenation catalysts are chromium, molybdenum, tungsten, platinum, palladium, rhodium, cobalt, nickel and ruthenium, their oxides, and combinations thereof such as, for instance, the oxides of cobalt or molybdenum in admixture and including cobalt molybdate. The preferred hydrogenation catalyst is palladium or RANEY nickel as well as other platinum group metals. Conveniently, the catalyst may be supported on carbon, for example charcoal.

Advantageously, the catalyst may be utilized in the presence of an inert solvent, for example, an alkanol such as methanol and ethanol, a hydrocarbon such as benzene, toluene, ethyl acetate and DMF. Most preferably, benzene is utilized.

The chemical reduction may be effected in a conventional manner; for example, with a metal such as iron, zinc or tin in an organic or inorganic acid such as acetic acid or hydrochloric acid, with stannous chloride in hydrochloric acid, with ferrous sulfate, with sodium dithionate, with sodium or ammonium sulfide or hydrosulfide. The conditions for the chemical reduction are not critical. Preferably, it is effected at a temperature in the range of from about room temperature to the reflux temperature of the mixture in the presence of a solvent such as water or a water miscible solvent, for example, an alkanol such as methanol, ethanol or tetrahydrofuran.

While, in general, the substituents represented by R₁ and R₂ are unaffected by the condensation and subsequent reduction, in certain cases they may be affected. For instance, during the condensation, a carboxyl group may be converted to an ester group and a phenolic hydroxyl group may be converted to a phenolic ether. Also, for instance, a dialkoxymethyl group can be retained or hydrolyzed. In the presence of acid, the dialkoxymethyl group is cleaved while, if no acid is present, it is retained.

Upon completion of the reduction, the end products, for example, indole, may be recovered utilizing conventional means such as crystallization, distillation or steam distillation. The indoles of formula I, are well documented in the literature and are useful for many purposes, for example, as intermediates in the preparation of amino acids, alkaloids and tryptamines. Thus, for example, indole, 6-methoxyindole and 5-benzoyloxyindole can be utilized as intermediates in the preparation of tryptophan, reserpine and serotonin, respectively.

The following Examples illustrate the in-

70

75

80

85

90

95

100

105

110

115

120

125

130

B) The condensation:

A 100 ml three-necked flask fitted with a thermometer and a 15 cm VIGREUX column connected to a descending condenser and a receiver with a nitrogen inlet was charged with 24.32 g of 5-benzyloxy-2-nitrotoluene, 23.0 g of N,N-dimethylformamide diethyl acetal and 25 ml of N,N-dimethylformamide. The flask was then immersed in an oil bath at 160° for 40 hours. The pot temperature was maintained above 140° by continuous distillation of the ethanol as it was formed.

The volatile components were removed under reduced pressure on a rotary evaporator. The red solid residue, crystallized from 300 ml of ether and 25 ml of benzene, yielded 23.3 g (78%) of *trans*-5-benzyloxy- β -dimethylamino-2-nitrostyrene as red needles having a melting point of 97.5—99°.

Anal. Calcd. for $C_{17}H_{18}N_2O_4$:

C, 68.44; H, 6.08; N, 9.39

Found:

C, 68.73; H, 6.13; N, 9.46

EXAMPLE 6

A solution containing 15.0 g of *trans*-5-benzyloxy- β -dimethylamino-2-nitrostyrene in 250 ml of 80% ethanol (N,N-dimethylformamide) and 1 teaspoonful of RANEY nickel were shaken under a hydrogen atmosphere in a PARR apparatus until hydrogen absorption ceased. The catalyst was removed by filtration. The solvents were removed under a vacuum. The residue was sublimed and the sublimate was crystallized from ether/(petroleum ether) to yield 5.1 g (45%) of 5-benzyloxindole as white needles having a melting point of 103—105°.

EXAMPLE 7

A 100 ml three-necked flask fitted with a thermometer and a 15 cm VIGREUX column connected to a descending condenser and a receiver with a nitrogen inlet was charged with 18.1 g of 3-methyl-4-nitrobenzoic acid, 37.6 g of N,N-dimethylformamide diethyl acetal and 25 ml of N,N-dimethylformamide. The flask was then immersed in an oil bath at 100° for 4.5 hours. The pot temperature was maintained above 135° by continuous distillation of the ethanol formed during the condensation.

The volatile components were removed by vacuum distillation. After trituration with petroleum ether, the residue crystallized to give 18.5 g (70%) of *trans*-3-(β -dimethylaminovinyl)-4-nitrobenzoic acid ethyl ester as a red solid having a melting point of 55—56.5°.

Anal. Calcd. for $C_{17}H_{18}N_2O_4$:

C, 59.08; H, 6.10; N, 10.60

Found:

C, 59.02; H, 6.00; N, 10.63

EXAMPLE 8

A solution containing 7.5 g of *trans*-3-(β -

dimethylaminovinyl)-4-nitrobenzoic acid ethyl ester in 250 ml of absolute ethanol and 715 mg of 10% palladium on carbon were shaken under 3.5 atmospheres of hydrogen in a PARR apparatus until hydrogen absorption ceased. The catalyst was removed by filtration and the filtrate was dried. The residue was applied to a column containing 100 g of magnesia/(silica gel). The fractions containing the product (eluted with benzene) were combined. Crystallization from ether/(petroleum ether) yielded 2.1 g (39%) of 5-indolecarboxylic acid ethyl ester as white crystals having a melting point of 95—96°.

Anal. Calcd. for $C_{11}H_{11}NO_2$:

C, 69.82; H, 5.86; N, 7.40

Found:

C, 70.14; H, 5.87; N, 7.45

EXAMPLE 9

A 250 ml three-necked flask fitted with a thermometer and a 15 cm VIGREUX column connected to a descending condenser and receiver with a nitrogen inlet was charged with 17.16 g of 2-chloro-6-nitrotoluene, 24 g of N,N-dimethylformamide diethyl acetal and 100 ml of N,N-dimethylformamide. The flask was immersed in an oil bath, preheated to 160°, for 6 hours. The pot temperature was maintained at about 140° by continuous distillation of the ethanol formed during the condensation.

The volatile components were removed by vacuum distillation at 25°/3 mm and the product was distilled to give 20.2 g (89%) of *trans*-6-chloro- β -dimethylamino-2-nitrostyrene as a dark red liquid having a boiling point of 111°/0.03 mm.

Anal. Calcd. for $C_{11}H_{11}ClN_2O_2$:

C, 52.99; H, 4.89; Cl, 15.67; N, 12.36

Found:

C, 53.18; H, 4.57; Cl, 15.75; N, 12.23

EXAMPLE 10

To a solution containing 10.40 g of *trans*- β -dimethylamino-6-chloro-2-nitrostyrene in 250 ml of benzene in a 500 ml PARR bottle was added half a teaspoonful of RANEY-nickel. The suspension was shaken under an initial hydrogen pressure of 3.5 atmospheres until the absorption of hydrogen ceased. The catalyst was removed by filtration and was washed several times with benzene. The benzene filtrate was then extracted with three 75 ml portions of 1M sulfuric acid and two 100 ml portions of water. The aqueous phases were back-washed with 125 ml of benzene in a countercurrent manner. The combined benzene phases were dried (K_2CO_3), filtered, and evaporated to give 5.4 g of dark green oil which, on distillation, yielded 4.75 g of a yellow liquid having a boiling point of 116°/2 mm. After redistillation there were obtained 4.41 g (63%) of 4-chloroindole as a

85 ml of concentrated ammonia. The resulting mixture was heated at reflux for 15 minutes and the precipitate which formed was removed by filtration. The filtrate was concentrated by evaporation and then extracted with three 200 ml portions of carbon tetrachloride. The combined organic phases were dried (Na_2SO_4), filtered and evaporated. The residue was percolated through a dry column of alumina with 5% benzene/hexane. The fractions were combined and the solvents removed to give 450 mg of a white solid. The material was crystallized from 8 ml of petroleum ether to give 277 mg of 5,6-dimethylindole as white needles having a melting point of 64.5—65.5°.

EXAMPLE 16

A 250 ml three-necked flask fitted with a thermometer and a 15 cm VIGREUX column connected to a descending condenser and receiver with a nitrogen inlet was charged with 20.00 g of 5-fluoro-2-nitrotoluene, 56.0 g of 85% N,N-dimethylformamide diethyl acetal and 100 ml of N,N-dimethylformamide. The flask was immersed in an oil bath, preheated to 160°, for 3.5 hours. The pot temperature was maintained above 140° by continuous distillation of the ethanol formed.

The volatile components were removed by vacuum distillation at 25°/0.5 mm and the residual dark red solid was crystallized from 70 ml of ether/(petroleum ether) to give 20.55 g of red needles having a melting point of 52—55°. The mother liquor, after removal of the solvents and distillation, yielded an additional 4.24 g of red solid having a melting point of 56—58°. The total yield was 24.79 g (92%). A portion of the material was recrystallized to give *trans*- β -dimethylamino - 5 - fluoro - 2 - nitrostyrene as red crystals having a melting point of 56—58°. Anal. Calcd. for $\text{C}_{10}\text{H}_{11}\text{FN}_2\text{O}_2$:

C, 57.14; H, 5.28; F, 9.03; N, 13.32

Found:

C, 57.05; H, 5.36; F, 8.72; N, 13.39

EXAMPLE 17

To a solution of 10.51 g of *trans*- β -dimethylamino - 5 - fluoro - 2 - nitrostyrene in 250 ml of benzene in a 500 ml PARR bottle was added half a teaspoonful of RANEY nickel. The suspension was shaken under an initial hydrogen pressure of 3.5 atmospheres until the absorption of hydrogen ceased. The catalyst was removed by filtration and washed several times with benzene. The benzene filtrate was then extracted with two 100 ml portions of 1M sulfuric acid, two 150 ml portions of water and 150 ml of 10% sodium bicarbonate solution. The aqueous phases were back-washed with 100 ml of benzene in a countercurrent manner. The combined benzene phases were dried (Na_2SO_4), filtered and evaporated to give 5.23 g of a brown solid.

Distillation (b.p. 85°/0.5 mm) yielded 5.01 g of a yellowish solid which, upon crystallization from pentane, yielded 2.36 g of 5-fluoroindole as white leaflets having a melting point of 46.5—47°. The mother liquor was percolated through 10 g of alumina and the product eluted with ether. Sublimation of this material gave an additional 1.07 g of product having a melting point of 46—47°. Thus, the total yield was 3.44 g (51%).

EXAMPLE 18

A 250 ml three-necked flask fitted with a thermometer and a 15 cm VIGREUX column connected to a descending condenser and receiver with a nitrogen inlet was charged with 11.18 g of 4-methyl-3-nitrobenzaldehyde dimethyl acetal, 11.8 g of N,N-dimethylformamide diethyl acetal and 50 ml of N,N-dimethylformamide. The flask was immersed in an oil bath, preheated to 160°, for 8 hours. The pot temperature was maintained above 140° by continuous distillation of the ethanol formed.

The volatile components were removed by vacuum distillation at 25°/0.5 mm. The dark red solid residue was triturated with cold methanol. The remaining solid was crystallized from 30 ml of ether/pentane to yield 7.22 g of *trans* - 4 - (β - dimethylaminovinyl) - 3 - nitrobenzaldehyde dimethyl acetal having a melting point of 67—68.5°. The residue, obtained after evaporation of the mother liquor, was crystallized from 5 ml of ether/pentane to give an additional 0.57 g of product having a melting point of 66.5—68.0°. Thus, the total yield was 7.79 g (55%).

Anal. Calcd. for $\text{C}_{15}\text{H}_{14}\text{N}_2\text{O}_4$:

C, 58.63; H, 4.81; N, 10.52

Found:

C, 58.69; H, 4.75; N, 10.40

EXAMPLE 19

To a solution containing 5.31 g of *trans* - 4 - (β - dimethylaminovinyl) - 3 - nitrobenzaldehyde dimethyl acetal in 250 ml of benzene in a 500 ml PARR bottle was added half a teaspoonful of RANEY nickel. The suspension was shaken under an initial hydrogen pressure of 3.5 atmospheres until the absorption of hydrogen ceased. The catalyst was removed by filtration and was washed several times with benzene. The residue, obtained by the evaporation of the benzene filtrate, was chromatographed on 150 g of alumina. The fractions eluted with 20% benzene/hexane followed by ether were combined and rechromatographed on 300 g of alumina. The fractions eluted with ether were combined (1.33 g) and crystallized from ether/pentane to give 0.76 g (26%) of 6-formylindole having a melting point of 127—128.5°.

EXAMPLE 20

To a solution containing 6.65 g of *trans* -

ceiver with a nitrogen inlet was charged with 16.7 g of 5-methoxy-2-nitrotoluene, 32.3 g of N,N-dimethylformamide diethyl acetal and 100 ml of N,N-dimethylformamide. The flask was then immersed in an oil bath, preheated to 165°, for 22 hours. The pot temperature was maintained above 140° by continuous distillation of the ethanol formed.

The volatile components were removed by vacuum distillation at 25°/0.5 mm. The resulting dark red solid residue was crystallized from 100 ml of ether and 75 ml of petroleum ether and yielded 17.0 g of *trans*- β -dimethylamino - 5 - methoxy - 2 - nitrostyrene as red crystals having a melting point of 67.5—69.5°. The residue, obtained after evaporation of the mother liquor, was triturated with 10 ml of ice-cold methanol. Recrystallization of the resulting solid (2.8 g) from 10 ml of methanol gave an additional 2.7 g of product having a melting point of 68—69°. Thus, the total yield was 19.7 g (89%).

Anal. Calcd. for $C_{11}H_{14}N_2O_3$:
C, 59.45; H, 6.35; N, 12.60

Found:
C, 59.53; H, 6.39; N, 12.65

EXAMPLE 26

To a solution containing 11.11 g of *trans*- β -dimethylamino - 5 - methoxy - 2 - nitrostyrene in 250 ml of benzene in a 500 ml PARR bottle were added 230 mg of 10% palladium on carbon. The suspension was shaken under an initial hydrogen pressure of 3.5 atmospheres until the absorption of hydrogen had ceased. The catalyst was removed by filtration and was washed several times with benzene. The benzene filtrate was then extracted with two 100 ml portions of 1M sulfuric acid, two 100 ml portions of water and 100 ml of 10% sodium bicarbonate solution. The aqueous phases were back-washed with 100 ml of benzene in a countercurrent manner. The combined benzene phases were dried (Na_2SO_4), filtered and evaporated to give 5.45 g of a brown solid. Distillation yielded 5.26 g (72%) of 5-methoxyindole as a slightly yellowish liquid having a boiling point of 108°/0.3 mm which crystallized on cooling to an off-white solid having a melting point of 56—57°.

EXAMPLE 27

A) The preparation of the starting material:

A solution containing 75.0 g of piperonal, 200 ml of glacial acetic acid and 1 ml of concentrated hydrochloric acid was shaken with 4 g of 10% palladium on carbon in an autoclave under an initial hydrogen pressure of 35 atmospheres until hydrogen absorption ceased. The catalyst was removed by filtration.

The filtrate was transferred to a three-necked flask fitted with a thermometer, mechanical stirrer and a dropping funnel. A solu-

tion containing 80.0 ml of concentrated nitric acid in 200 ml of glacial acetic acid was added to the reaction vessel with stirring over a period of 1 hour. The reaction vessel was maintained below 10° by means of an ice-acetone bath. After the addition was complete, the reaction mixture was allowed to reach room temperature and was then poured over a mixture of sodium hydroxide and ice. The resulting suspension was extracted with four 1000 ml portions of methylene chloride. The combined organic phases were dried (Na_2SO_4), filtered and evaporated to give a yellow solid which, after crystallization from 300 ml of ethanol, gave 76.5 g (84%) of 4,5-methylenedioxy - 2 - nitrotoluene as yellow needles having a melting point of 85—86.5°.

B) The condensation:

A 250 ml three-necked flask fitted with a thermometer and a 15 cm VIGREUX column connected to a descending condenser with a receiver and a nitrogen inlet was charged with 18.1 g of 4,5-methylenedioxy-2-nitrotoluene, 20 g of N,N-dimethylformamide diethyl acetal and 100 ml of N,N-dimethylformamide. The flask was immersed in an oil bath at 165° for 17.5 hours. The pot temperature was maintained above 140° by continuous distillation of the ethanol formed.

The volatile components were removed by vacuum distillation at 25°/0.05 mm. The residue was crystallized from 300 ml of ethanol to give 17.0 g (72%) of *trans*- β -dimethylamino - 4,5 - methylenedioxy - 2 - nitrostyrene as red-brown crystals having a melting point of 114—116°.

Anal. Calcd. for $C_{11}H_{12}N_2O_3$:
C, 55.93; H, 5.12; N, 11.86

Found:
C, 56.09; H, 5.17; N, 11.56

EXAMPLE 28

A solution containing 11.83 g of *trans*- β -dimethylamino - 4,5 - methylenedioxy - 2 - nitrostyrene in 250 ml of benzene was shaken with 1 teaspoonful of RANEY nickel under an initial hydrogen pressure of 3.5 atmospheres until hydrogen absorption ceased. The catalyst was removed by filtration and washed several times with benzene. The filtrate and washings were washed with two 100 ml portions of 1M sulfuric acid, 100 ml of water and 100 ml of 10% sodium bicarbonate. The combined organic phases were dried (Na_2SO_4), filtered and evaporated to give 5.52 g of a brown solid. A solution of the residue in benzene was percolated through a column of alumina. The eluate, after evaporation of the solvent, was sublimed at 110°/0.2 mm to give 5.2 g of a white solid which, upon crystallization from (methylene chloride)/hexane, yielded 4.50 g. (50%) of 5,6-methylenedioxyindole as white needles having a melting point of 109.5—110.5°.

10%, palladium on carbon and the suspension was shaken under an initial hydrogen pressure of 7 atmospheres. After hydrogen absorption ceased (3 equivalents), the catalyst was filtered and washed with 2 liters of benzene. The combined filtrate and washings were concentrated to 2 liters *in vacuo* and the organic phase washed with three 300 ml portions of 1N sulfuric acid, 200 ml of 1N sodium hydroxide and 200 ml of water. The aqueous phases were back-washed in a countercurrent manner with 500 ml of benzene. The combined organic phases were dried (Na_2SO_4) and filtered through 280 g of silica gel. The filtrate was evaporated and the residue triturated with ether. The residual white solid was crystallized from 700 ml of benzene to give (in two crops) 24.5 g (28%) of 5,6-dimethoxyindole as white crystals, m.p. 154—155°.

EXAMPLE 35

In a 1 liter three-necked flask fitted with a thermometer and 8 cm VIGREUX distillation head connected to a descending condenser and receiver with a nitrogen inlet were placed 87.3 g of 4,5-dibenzoyloxy-2-nitrotoluene, 38.0 g of N,N-dimethylformamide dimethyl acetal and 250 ml of N,N-dimethylformamide. The solution was heated at 140° for 48 hours with continuous removal of the methanol as it formed. The volatile components were removed by vacuum distillation (bath temperature 65°/0.1 mm). Crystallization of the residue from methanol (2.5 liters) yielded (two crops) 86.8 g of a red solid, m.p. 99—100°.

An analytical sample, obtained from a previous experiment, was characterized as *trans* - 4,5 - dibenzoyloxy - β - dimethyl - amino-2-nitrostyrene, m.p. 99.5—101°.

Anal. Calcd. for $\text{C}_{24}\text{H}_{24}\text{N}_2\text{O}_4$:
C, 71.27; H, 5.98; N, 6.93

Found:
C, 71.09; H, 6.30; N, 6.83

EXAMPLE 36

To a solution of 10.11 g of *trans*-4,5-dibenzoyloxy - β - dimethylamino - 2 - nitro - styrene in 250 ml of benzene in a 500 ml PARR bottle was added a teaspoonful of RANEY nickel. The suspension was shaken under an initial hydrogen pressure of 3.5 atmospheres until the absorption of hydrogen ceased. The catalyst was removed by filtration and washed several times with benzene. The benzene filtrate was extracted with three 100 ml portions of 1N sulfuric acid, 250 ml of water, three 100 ml portions of 1N sodium hydroxide and 250 ml of water. The aqueous phases were back-washed in a countercurrent manner with 100 ml of benzene.

The combined organic phases were dried (Na_2SO_4), filtered and evaporated to give 7.67 g of a brown solid which was dissolved in a minimum amount of benzene and chromato-

graphed on 40 g of silica gel prepared in hexane. Eluted fractions [benzene/hexane (1:1)] were pooled according to thin layer chromatography. Evaporation of the solvents and recrystallization of the residue (5.8 g) from benzene/hexane yielded 4.34 g (54%) of 5,6-dibenzoyloxyindole as white needles, m.p. 112—113°.

EXAMPLE 37

A 100 ml three-necked flask fitted with a reflux condenser with a nitrogen inlet was charged with 8.25 g of 4-methyl-3-nitrobenzaldehyde, 11.1 g of N,N-dimethylformamide diethyl acetal and 50 ml of N,N-dimethylformamide. The flask was immersed in an oil bath, preheated to 145°, for 45 minutes.

The volatile components were removed by vacuum distillation at 25°/0.5 mm. The dark red residue was triturated three times with 10 ml of petroleum ether. The solid residue gave, on crystallization from methanol, 5.47 g and, on recrystallization from 100 ml of (methylene chloride)/ether, 4.61 g of *trans*-4 - (β - dimethylaminovinyl) - 3 - nitrobenzaldehyde as red crystals having a melting point of 134—136°. The residue obtained from the mother liquors was crystallized from 12 ml of ethyl acetate to give an additional 2.21 g of product having a melting point of 134—136°. Thus, the total yield was 6.81 g (62%).

Anal. Calcd. for $\text{C}_{11}\text{H}_{11}\text{N}_2\text{O}_3$:
C, 59.99; H, 5.49; N, 12.72
Found:
C, 60.23; H, 5.22; N, 12.66

EXAMPLE 38

In a 100 ml three-necked flask fitted with a thermometer and 8 cm VIGREUX distillation head connected to a descending condenser and receiver with a nitrogen inlet were placed 6.85 g (0.05 mol) of *o*-nitrotoluene, 7.25 g (0.05 mol) of N-formylpyrrolidine dimethyl acetal and 25 ml of N,N-dimethylformamide. The flask was immersed in an oil bath at 160° for 1 hour during which time 2.8 ml of methanol distilled. Volatile components were removed by vacuum distillation from a CLAISEN flask. A portion of the residue was distilled with partial decomposition in a short-path distillation flask (bath 150°/0.1 mm). The distillate was then vaporized twice in a molecular still (bath 110°/0.04 mm), discarding a small amount of fore-run each time. In this way, 560 mg of analytically pure *trans* - 2 - nitro - β - pyrrolidinostyrene were obtained as a red liquid.

Anal. Calcd. for $\text{C}_{12}\text{H}_{11}\text{N}_2\text{O}_2$:
C, 66.03; H, 6.47; N, 12.84
Found:
C, 65.89; H, 6.45; N, 12.79

EXAMPLE 39

To a 100 ml three-necked flask fitted with

of *trans* - β - dimethylamino - 5 - methoxy - 2-nitrostyrene, m.p. 68.5—69.5°.

EXAMPLE 44

A solution of 3.0 g (0.018 mol) of 3-methyl-4-nitro-anisole, 5.1 g (0.020 mol) of N,N-dimethylformamide dicyclohexyl acetal and 25 ml of N,N-dimethylformamide was heated at reflux under a nitrogen atmosphere for 40 hours and was then transferred to a CLAISEN flask. Vacuum distillation afforded, after removal of the volatile components, 1.89 g of a red liquid (b.p. 158°/0.04 mm) which crystallized on scratching to give a solid, m.p. 61—64°. Recrystallization from 10 ml of ether and 7 ml of petroleum ether gave 1.46 g (36%) of *trans* - β - dimethylamino - 5-methoxy-2-nitrostyrene, m.p. 67.5—69°.

EXAMPLE 45

A solution of 16.71 g (0.10 mol) of 3-methyl-4-nitro-anisole, 30.00 g (0.11 mol) of N,N-dimethylformamide dibenzyl acetal and 50 ml of N,N-dimethylformamide was heated at reflux under a nitrogen atmosphere for 17 hours and was then transferred to a CLAISEN flask. Vacuum distillation afforded, after removal of the volatile components, 9.42 g of a red liquid (b.p. 158°/0.10 mm) which gave a tacky solid upon scratching. Recrystallization from 150 ml of ether/(petroleum ether) gave, in two crops, 7.15 g (32%) of *trans*- β -dimethylamino - 5 - methoxy - 2 - nitrostyrene, m.p. 68.0—69.5°.

EXAMPLE 46

A solution of 8.35 g (50 mmol) of 3-methyl-4-nitro-anisole, 8.76 g (75 mmol) of N,N-dimethylformamide ethylene acetal (2-dimethylamino-1,3-dioxolane) and 25 ml of N,N-dimethylformamide was heated at 150° under a nitrogen atmosphere for 53 hours and was then transferred to a CLAISEN flask. Vacuum distillation afforded, after removal of the volatile components, 4.00 g of a red liquid (b.p. 149°/0.07 mm) which formed a gummy solid on scratching. Crystallization from 15 ml of methanol gave 1.57 g (14%) of *trans*- β - dimethylamino - 5 - methoxy - 2 - nitro - styrene, m.p. 68—69°.

EXAMPLE 47

In a 500 ml three-necked flask fitted with a thermometer and mechanical stirrer were placed 19.2 g (0.10 mol) of *trans*- β -dimethylamino-2-nitrostyrene, 100 ml of ethanol and 100 ml of glacial acetic acid followed by 41.9 g (0.75 mol) of purified iron powder over a period of 5 minutes. The suspension was stirred for 2 hours during which time the temperature rose to 45° (the temperature was controlled by a water bath). Then 30 ml of 1N hydrochloric acid were added. The red colour discharged and the temperature rose to about 45°. The mixture was allowed to

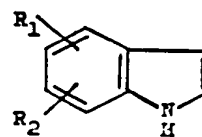
stand for 18 hours and was then poured on to 1 liter of ice-water. To the resulting slurry were added 250 ml of benzene and then both phases were filtered through a bed of diatomaceous silica. The benzene layer was separated and the aqueous layer extracted once more with 200 ml of benzene. The combined benzene extracts were washed successively with two 200 ml portions of 0.5N sulfuric acid and 100 ml of 10% potassium carbonate. The aqueous phases were back-washed in a countercurrent manner with 100 ml of benzene. The combined organic phases were dried (Na₂SO₄), filtered and evaporated to give 4.2 g of a brown solid which was dissolved in a minimum amount of benzene and chromatographed on 50 g of alumina. Eluted fractions containing indole [(petroleum ether)/benzene, (9:1)] were pooled according to the thin layer chromatography. Evaporation of the solvents and sublimation of the residue (40—50° oil bath/0.03 mm) yielded 2.02 g (17%) of indole as white plates, m.p. 51.5—52.5°.

EXAMPLE 48

To a stirred solution of 19.2 g (0.10 mol) of *trans* - β - dimethylamino - 2 - nitro - styrene in 500 ml of water and 200 ml of methanol was added portionwise over 5 minutes a mixture of 55.0 g (0.315 mol) of sodium dithionite and 28.0 g (0.20 mol) of potassium carbonate while maintaining the temperature at 60—65° by means of a water bath. Since a suspension formed, 300 ml of methanol were added and stirring was continued for 0.75 hour. To the mixture were added 20 ml of 30% ammonium hydroxide and, after removal of the methanol with a rotary evaporator, an additional 60 ml of 30% ammonium hydroxide. The solution was then extracted with three 400 ml portions of benzene. The organic phases were back-washed in a countercurrent manner with 100 ml of water. The combined organic phases were dried (Na₂SO₄), filtered and evaporated to give 3.5 g of a dark brown solid which was dissolved in a minimum amount of benzene and chromatographed on 60 g of alumina. Eluted fractions (petroleum ether) containing indole were pooled according to thin layer chromatography. Evaporation of the solvents and sublimation of the residue (2.4 g) yielded 2.14 g (18%) of indole, m.p. 50—52°.

WHAT WE CLAIM IS:—

1) A process for the manufacture of indoles of the general formula



(I)

65

70

75

80

85

90

95

100

105

110

115

wherein the condensation is effected in the presence of a polar aprotic solvent.

19) A process as claimed in claim 18, wherein the solvent is *N,N*-dimethylformamide, diethyleneglycol dimethyl ether or hexamethylphosphortriamide.

20) A process as claimed in any one of claims 17 to 19 inclusive, wherein the condensation is conducted at a temperature in the range of from 100°C to 160°C.

21) A process as claimed in any one of claims 17 to 20 inclusive, wherein at least one of R_1 and R_2 represents other than methyl when one of R_1 and R_2 represents hydrogen and the other represents hydrogen or methyl in the 3-position.

22) A process as claimed in claim 21, wherein R_1 and R_2 independently represent hydrogen, lower alkyl, aryl, hydroxy, lower alkoxy, aryl-lower alkoxy, aryloxy, acyloxy, formyl, aroyl, hydroxymethyl, aryl-hydroxymethyl, carboxy, lower alkoxycarbonyl, carbamoyl, halogen, amino, mono-lower alkylamino, di-lower alkylamino, lower alkoxy carbonylamino, aryl-lower alkoxycarbonylamino, acylamino, *N*-lower alkylacylamino, di-lower alkylformamidino or dimethoxymethyl or R_1 and R_2 together represent lower alkylenedioxy and R_3 and R_6 independently represent lower alkyl or R_3 and R_6 together represent lower alkylene.

23) A process as claimed in claim 21 or claim 22, wherein R_1 and R_2 independently represent hydrogen, lower alkyl, hydroxy lower alkoxy, aryl-lower alkoxy, acyloxy, formyl, aroyl, halogen, amino or acylamino or R_1 and R_2 together represent lower alkylenedioxy.

24) A process as claimed in any one of claims 21 to 23 inclusive, wherein R_1 and R_2 each represent hydrogen.

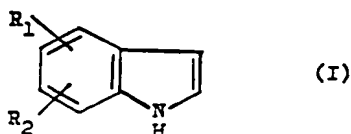
25) A process as claimed in any one of claims 21 to 24 inclusive, wherein R_3 and R_6 each represent lower alkyl.

26) A process as claimed in any one of claims 21 to 23 inclusive and claim 25, wherein R_3 and R_6 each represent methyl.

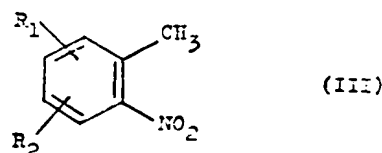
27) A process as claimed in any one of claims 17 to 20 inclusive, wherein R_1 and R_2 each represent methyl and one of R_1 and R_2 represents hydrogen and the other represents hydrogen or methyl in the 3-position.

28) A process as claimed in claim 27, wherein R_3 and R_6 independently represent lower alkyl or R_3 and R_6 together represent lower alkylene.

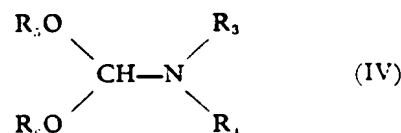
29) A process for the manufacture of indoles of the general formula



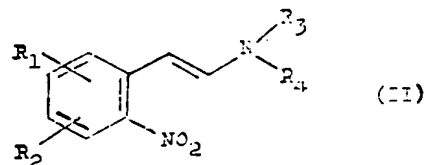
wherein R_1 and R_2 have the significance given in claim 1, which process comprises condensing an *ortho*-nitrotoluene of the general formula



wherein R_1 and R_2 have the significance given in claim 1, with a formamide acetal of the general formula



wherein R_3 and R_4 have the significance given in claim 1 and R_5 and R_6 have the significance given in claim 17, and treating the resulting *ortho*-nitro- β -aminostyrene of the general formula



wherein R_1 , R_2 , R_3 and R_4 have the significance given in claim 1, with a reducing agent.

30) A process as claimed in claim 29, wherein the condensation is effected in the presence of a polar aprotic solvent.

31) A process as claimed in claim 30, wherein the solvent is *N,N*-dimethylformamide, diethyleneglycol dimethyl ether or hexamethylphosphortriamide.

32) A process as claimed in any one of claims 29 to 31 inclusive, wherein the condensation is conducted at a temperature in the range of from 100°C to 160°C.

33) A process as claimed in any one of claims 29 to 32 inclusive, wherein the *ortho*-nitro- β -aminostyrene of formula II is hydrogenated in the presence of a suitable hydrogenation catalyst.

34) A process as claimed in claim 33, wherein the hydrogenation catalyst consists of chromium, molybdenum, tungsten, platinum, palladium, rhodium, cobalt, nickel or ruthenium, their oxides or combinations thereof.

35) A process as claimed in claim 34, wherein palladium or RANEY nickel is used as the hydrogenation catalyst.

clusive, wherein R_1 and R_2 each represent hydrogen.

57) An *ortho*-nitro- β -aminostyrene as claimed in any one of claims 53 to 56 inclusive, wherein R_3 and R_4 each represent lower alkyl.

58) An *ortho*-nitro- β -aminostyrene as claimed in any one of claims 53 to 55 in-

clusive and claim 57, wherein R_3 and R_4 each represent methyl.

10

For the Applicants,
CARPMAELS & RANSFORD,
Chartered Patent Agents,
24, Southampton Buildings, Chancery Lane,
London, WC2A 1AZ.

Printed for Her Majesty's Stationery Office, by the Courier Press, Leamington Spa, 1972.
Published by The Patent Office, 25 Southampton Buildings, London, WC2A 1AY, from
which copies may be obtained.

80

85

90

95

100

105

110

115

120

**This Page is Inserted by IFW Indexing and Scanning
Operations and is not part of the Official Record**

BEST AVAILABLE IMAGES

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images include but are not limited to the items checked:

- ☒ **BLACK BORDERS**
- ☐ **IMAGE CUT OFF AT TOP, BOTTOM OR SIDES**
- ☐ **FADED TEXT OR DRAWING**
- ☐ **BLURRED OR ILLEGIBLE TEXT OR DRAWING**
- ☐ **SKEWED/SLANTED IMAGES**
- ☐ **COLOR OR BLACK AND WHITE PHOTOGRAPHS**
- ☐ **GRAY SCALE DOCUMENTS**
- ☐ **LINES OR MARKS ON ORIGINAL DOCUMENT**
- ☐ **REFERENCE(S) OR EXHIBIT(S) SUBMITTED ARE POOR QUALITY**
- ☐ **OTHER:** _____

IMAGES ARE BEST AVAILABLE COPY.

As rescanning these documents will not correct the image problems checked, please do not report these problems to the IFW Image Problem Mailbox.